PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/000033	07.01.2005	07.01.2004

International Patent Classification (IPC) or both national classification and IPC
B01J19/00, C12Q1/68

Applicant
SOLEXA LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/000033

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/000033

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1,17-19,37,51,54,57-60
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-60
Industrial applicability (IA)	Yes:	Claims	1-60
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2005/000033

Re Item IV
Lack of unity of invention

This Authority considers that there are 2 inventions covered by the claims indicated as follows:

I: Claims 1-36, 51-56 (in part) and 57-60, directed to method of preparing specific hydrogels on support and use thereof in arrays.
II: Claims 37-50 and 51-56 (in part), directed to method of modifying a molecular array.

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

A) The "same" or "corresponding" technical feature between these independent claims is a (molecular) array.

This feature is a priori already known from the art, since (molecular) arrays are quite common in biochemical, pharmaceutical and diagnostic research.

Therefore, this feature is not a special (new and inventive) technical feature. Thus, no "same" or "corresponding" special technical features could be found between the abovementioned inventions, as required by Rule 13.2 PCT.

B) The problem to be solved by the first (alleged) invention appears to be the provision of a general method for modifying a solid support to allow the preparation of supports useful in the preparation of arrays (page 5, lines 30-32 of the present application).

The problem solved by the second (alleged) invention appears to be the provision of arrays which have a lesser tendency to interact non-specifically with other molecules than those available in prior art (page 5, lines 24-30).

No common problem could be found which could serve as the general inventive concept required by Rule 13.1 PCT.
Consequently, these (alleged) inventions are not unitary according to Rule 13 PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 01/23082 A (NANOGEN, INC) 5 April 2001 (2001-04-05)

D2: WO 00/31148 A (MOTOROLA, INC; MCGOWEN, JOHN, A; BEUHLER, ALLYSON, J) 2 June 2000 (2000-06-02)

D3: WO 01/01143 A (MOTOROLA INC; JOHNSON, TRAVIS; MCGOWEN, JOHN; BEUHLER, ALLYSON; BRUSH,) 4 January 2001 (2001-01-04)

D4: US-A-5 858 653 (DURAN ET AL) 12 January 1999 (1999-01-12)

D5: WO 2004/073843 A (MCMASTER UNIVERSITY; CHILDS, RONALD, F; FILIPE, CARLOS; GHOSH, RAJA; M) 2 September 2004 (2004-09-02)

D6: WO 02/059372 A (BIOCEPT INC ; DONG XIAOFAN (US); FAGNANI ROBERTO (US); HAHN SONNKAP (U) 1 August 2002 (2002-08-01)

D7: US-A-5 948 621 (GABER BRUCE P ET AL) 7 September 1999 (1999-09-07)

D8: WO 99/61653 A (ZEBALA JOHN A ; SYNTRIX BIOCHIP (US)) 2 December 1999 (1999-12-02)

D9: US-A-6 077 674 (TOM-MOY MAY ET AL) 20 June 2000 (2000-06-20)

D10: KARTALOV ET AL.: "Polyelectrolyte Surface Interface for Single-Molecule Fluorescence Studies of DNA Polymerase" BIOTECHNIQUES, vol. 34, no. 3, 2003, pages 505-510, XP002310467

Invention I

Novelty and Inventive Step (Art. 33(1) and (2), Art. 33(3) PCT)

Note that in claim 1, the moiety "C" is a group capable of reaction with a compound, see PCT international search and preliminary examination guidelines §5.25, which amounts to basically any chemical moiety which is not completely unreactive.

1.1 D1 (see passages cited in the Search Report) discloses a permeation layer coated microarray, wherein the permeation layer comprises functional groups for attaching high densities of derivatized biomolecules (page 13, 1st paragraph). These groups have

formula P-X-R, in which P is preferably polymerizable and can be amide, X can be alkyl, R is the attaching moiety, such as halo-acetamide (of which the advantage of not requiring activation is specifically mentioned on page 17).

In example 2, experiment 1, a hydrogel permeation layer is formed on a microarray by crosslinking acrylamide with methylene-bisacrylamide (compound falling under definition of formula (I)).

In example 5, acrylamide, methylene bis-acrylamide and 3-aminopropyl methylacrylamide hydrochloride (compound of formula (II)) monomers are reacted onto a silanized microchip to form the permeation layer.

D1, therefore, destroys the novelty of independent claim 1.

The hydrogel layers are meant to further anchor biomolecules for use as addressable arrays (for interrogation of immobilized molecules of interest).
D1, thus, destroys the novelty of independent claims 1,17,19,51,54 and 57, contrary to the requirements of Article 33(1) and (2) PCT.

1.2 D1 provides a general method for modifying a solid support to allow the preparation of supports useful in the preparation of arrays. It therefore discloses the same technical features as the independent claims and solves the same problem as the present application. The features of all other claims belonging to invention 1 do not appear to further contribute to solving this problem in any surprising manner and therefore do not involve an inventive step (Article 33(3) PCT).

2. D2 (see passages cited in the Search Report) describes the preparation of hydrogel arrays made from polyacrylamide reactive prepolymers. Example 3 describes coating of surfaces with a solution comprising the comonomers acrylamide and glycidyl methacrylate (compound (II)) and polymerizing them into a hydrogel. D2 also discloses pre silanizing the silicon supports (using methacryloxypropyltrimethoxysilane) and applying thin layers of between 1 to 40 microns. Therefore, also D2 destroys the novelty of claims 1,17-18, 57-60.

3.1 D3 (see passages cited in the Search Report) describes acrylamide monomer based hydrogel arrays as binding layers for biological molecules.

Example 3 describes coating of surfaces with a solution comprising the comonomers acrylamide and glycidyl methacrylate (compound (II)) and polymerizing them into a

hydrogel. The fact that the prepolymer is reacted also with acrylic acid does not change the fact that D3 discloses a method comprising all technical features of claim 1.

The hydrogel layers are meant to further anchor biomolecules for use as addressable arrays (for interrogation of immobilized molecules of interest).
D1, thus, destroys the novelty of independent claims 1,17,19,51,54 and 57, contrary to the requirements of Article 33(1) and (2) PCT.

3.2 D1 provides a general method for modifying a solid support to allow the preparation of supports useful in the preparation of arrays. It therefore discloses the same technical features as the independent claims and solves the same problem as the present application. The features of all other claims belonging to invention 1 do not appear to further contribute to solving this problem in any surprising manner and therefore do not involve an inventive step (Article 33(3) PCT).

4. D4 (see passages cited in the Search Report) also discloses the technical features of the subject-matter of claims 1 and 17, contrary to the requirements of Article 33(1) and (2) PCT.

Invention II

Novelty and Inventive Step (Art. 33(1) and (2), Art. 33(3) PCT)

5. The terms polyelectrolyte and neutral polymers basically encompass all polymers. It is remarked that polypeptides (proteins) are polylectrolytes. Any array with immobilized biomolecules to which a protein is added destroys the novelty of the subject-matter of claim 37. Claim 37, therefore, is *a priori* not novel.

6.1 D6 (see passages cited in the Search Report) describes the synthesis of molecular arrays comprising a hydrogel as support, which may be treated with agents to reduce subsequent non-specific adherence of assay reagents, target molecules or other materials. One of the specifically mentioned reagents are activated polyethylene glycol polymers.
Thus, D6 destroys the novelty of independent claims 37,51 and 54.

6.2 D6 not only discloses the technical features of the independent claims, it also discloses the performance of the modification step for the same purpose as the present application. No surprising effects/advantages of the subject-matter of the dependent claims could be determined. Technical features not relevant for solving the problem may be disregarded for the purpose of determining inventive step. As a result, the subject-matter of none of the dependent claims, if not already disclosed by D6, can be presently considered to involve an inventive step.

7. Similar considerations apply to D7, where BSA (polyelectrolyte) is used to block non-specific binding on a silane coated array.

8. D8 does not disclose adding neutral polymers or polyelectrolytes to molecular arrays in order to inhibit non-specific attachment. It does, however, disclose the addition of a large number of different polymers (as photoresists) to molecular arrays of many different kinds and on many different types of surfaces (see passages cited in Search Report; page 38 (halfway) to page 44, first paragraphs; page 28; page 33, lines 3-10). As such D8 is novelty destroying for all independent claims and many dependent claims.

9. D9 (see passages cited in the Search Report) generally discloses passivating areas on an array not containing oligonucleotide features on silane covered array slides. It is not specific on how this is done, but in the absence of any particular advantages over other possible deactivation methods, using polymers in general would appear to be one of the straightforward alternatives the skilled person would choose from. Therefore the independent claims 37,51 and 54 are also not inventive over D9.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 2004/073843	02.09.2004	29.01.2004	19.02.2003